Review Article

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Vitamin A as a key regulator of obesity & its associated disorders: Evidences from an obese rat model

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During the last century, vitamin A has evolved from its classical role as a fat-soluble vitamin and attained the status of para-/autocrine hormone. Besides its well-established role in embryogenesis, growth and development, reproduction and vision, vitamin A has also been implicated in several other physiological processes. Emerging experimental evidences emphasize adipose tissue as an active endocrine organ with great propensity to continuous growth (throughout life). Due to various genetic and lifestyle factors, excess energy accumulates in adipose tissue as fat, resulting in obesity and other complications such as type 2 diabetes, hypertension, and cardiovascular disease. Recent *in vitro* and *in vivo* studies have shed light on vitamin A metabolites; retinaldehyde and retinoic acid and participation of their pathway proteins in the regulation of adipose tissue metabolism and thus, obesity. In this context, we discuss here some of our important findings, which establish the role of vitamin A (supplementation) in obesity and its associated disorders by employing an obese rat model; WNIN/Ob strain.

Key words Adipose tissue - inflammation - insulin resistance - muscle - obesity - retinoids - supplementation

Introduction

Vitamin A exists in three physiologically active forms (Vitamers) namely retinol (alcohol), retinal (aldehyde) and retinoic acid (acid), which are collectively known as retinoids (which also include synthetic compounds having some biological activity of vitamin A). Vitamin A is an important fat-soluble micronutrient essential for embryonic development, haematopoiesis, neuronal cell growth, reproduction, immune function, vision, *etc.*[1-5]. In addition to its wide range of physiological functions, extensive research during the past two decades labelled vitamin A as a key regulator of adipose tissue biology[6-8]. The recent studies addressing the role of vitamin A metabolic pathway to various physiological processes by way of gene knockout models (ALDH, CRBP, LRAT, RBP4, RDH, BCMO, STRA6 and RetSat)[9-16] mark the plethora of events regulated by vitamin A. In this context, the main focus of this review is to highlight certain important findings, which unveiled the role of vitamin A on obesity and its associated disorders particularly dyslipidaemia, insulin resistance and retinal degeneration from an obese rat model of WNIN/Ob strain.

Obesity and role of adipose tissue

Obesity, the chronic, highly prevalent abnormal metabolic condition affecting the millions of lives

across the globe with enormous economic consequences has been aptly identified as "globesity"[17]. It has been predicted that by 2030 adults will contribute 1.12 billions to obese and 2.16 billions to overweight population worldwide[18]. Obese people are at a greater risk for co-morbidity and mortality due to a variety of medical complications including type 2 diabetes (T2D), hypertension, dyslipidaemia, cardiovascular disease (CVD), sleep apnoea and some types of cancers, apart from various psychological stresses including body image, disparagement, impaired quality of life and depression[19].

Though, the aethiopathogenesis of obesity is largely unclear, genetic and lifestyle factors are believed to determine the development and progression of the obesity. In obese condition, excess energy is deposited as fat in adipose tissue, particularly, white adipose tissue (WAT). WAT with its capability of accommodating the excess energy leads to an increased adipose tissue growth in obese people. Adipose tissue consists of several cell types including mature adipocytes, stromal vascular fractions consisting of pre-adipocytes, immune cells, vascular progenitor cells and endothelial cell. In humans, nearly 30 billion adipocytes are present during the development of infant to adolescent and this number can go up to 40-60 billion cells under abnormal conditions such as obesity, amounting to 0.5-1 per cent of total number of cells of a human body. Normally, the size of a mature adipocyte varies from 10 to 200 μm and accommodates 0.5-1μg of fat and maximum of 4 μg under abnormal metabolic condition. In a healthy individual, adipocyte mass accounts for approximately 20 per cent of body weight and fat mass may range from 2-3 to 60-70 per cent of body weight of a normal athletes and massively-obese individuals, respectively[20,21].

Biological link between adipose tissue and vitamin A

Besides liver, adipose tissue contains substantial amount of retinol and its metabolites. Tsutsumi *et al*[22] have shown that visceral and subcutaneous adipose depots reserve comparable amount of retinol (*i.e*. 6.4 and 6.9 μg retinol per gram tissue). They also found that in adipose tissues, retinol is stored mostly in free form, which accounts for 75 per cent, while esterified form accounts for only 25 per cent of total retinol stores[22].

Several studies have shown that adipose tissue plays an active role in the metabolism and homeostasis of vitamin A by taking-up circulatory chylomicron-bound (by lipoprotein lipase)/retinol binding protein (RBP)-bound retinol and converting retinol to physiologically - active metabolites *viz*. retinaldehyde (Rald) and retinoic acid (RA). Interestingly, WAT also expresses RBP at high levels, which further emphasizes its role in retinoid homeostasis. Adipocytes are reported to have complete machinery for the uptake, transport, esterification, hydrolysis, oxidation and degradation of retinoids such as RBP4 receptor; stimulated by retinoic acid (STRA6), lipoprotein lipase, cellular retinol binding proteins, retinol binding protein, lecithin:retinol acyltransferase, acyl CoA:retinol acyltransferase, hormone-sensitive lipase, short chain dehydrogenases/reductases, alcohol dehydrogenases and aldehyde dehydrogenases and cytochrome 450 enzyme; CYP26, *etc*. Thus, adipocytes store, metabolize and mobilize their retinol stores to meet both local and total body demands[23-25]. Apart from vitamin A homeostasis, adipose tissue also differentially expresses the retinoid X receptor and retinoic acid receptors of different subtypes (α, β and γ); the transcriptional regulator of vitamin A thereby suggesting that adipocytes are the potential targets for vitamin A action[26-28].

Obesity, inflammation and vitamin A

Growing evidences suggest that obesity is an abnormal metabolic condition associated with chronic low grade inflammation and altered intestinal microbiome, which are known to play a major role in this disease process[29,30]. Adipose tissue is proven to be the major contributor of inflammation and now it is well recognized as not just an inert energy reservoir, but functions as an endocrine organ and centre of immune modulation by virtue of secreting various adipokines such as leptin, adiponectin, adipsin, resistin, plasminogen activator inhibitor-1 and cytokines such as tumour necrosis factor α (TNF-α), interleukins (ILs), and monocyte chemoattractant protein (MCP). These adipokines and cytokines are the primary mediators of inflammation and implicated in the development of various obesity-associated inflammatory complications including insulin resistance, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, *etc*.[31-33].

Among various adipokines, leptin is secreted primarily by the adipose tissue and is identified as a

regulator of food intake and energy homeostasis[34]. Leptin is also recognized as a hormone with multiple physiological functions; especially linking obesity, immune functions and inflammation[35-38]. Kumar and Scarpace[39] have shown for the first time that retinoic acid downregulates the leptin mRNA in white adipose tissue[39]. Subsequently, many studies have demonstrated the negative transcriptional regulation of leptin gene by vitamin A and its metabolites in experimental models[40-42]. However, the impact of vitamin A supplementation on obesity, leptin and regulation of inflammation has not been addressed so far. Vitamin A and its metabolites are known to potentiate the immune system and functions including T-cell proliferation, B-cell activation, T helper cells (TH1 & TH2) balance and differentiation of regulatory T-cells (Treg cells)[43,44]. Role of vitamin A on immunity, its function on immune system and obesity under deficient and sufficient conditions have been extensively reviewed by Garcıa[45,46].

In humans, studies have shown the association between vitamin A intake and obesity. Zulet *et al*[47] have reported inverse relationship between vitamin A intake and adiposity in healthy adults aged between 18-22 yr. Other studies have also reported inverse correlation between serum retinol and body mass index in morbidly obese subjects[48-54]. Further, in obese subjects, adipose derived-inflammatory cytokines, such as leptin, serum amyloid A (SAA), TNF-α and IL-6 have been shown to be elevated[55,56]. Reichert *et al*[27] have observed abundant expression of retinoic acid synthesizing enzyme gene *Aldh1a1* in fat fads particularly subcutaneous and omental fat of healthy women. In *Aldh1a1* knockout mouse model deficiency of this gene impaired hepatic glucose production resulting in decreased fasting glucose levels[57]. Further, these mice, displayed higher uncoupling protein-mediated thermogenesis in white adipose tissue and thereby regulating energy homeostasis[58]. Discovery of adipose-derived retinol binding protein added a new insight into the role of vitamin A metabolic pathway protein on the regulation of insulin sensitivity[12]. Mills *et al*[59] have found a significant association between circulatory RBP, obesity and insulin resistance. They observed a two-fold increase in apo-RBP levels in obese subjects compared to non-obese counterparts. Several other studies have reported significant association between vitamin A status, circulatory RBP level, obesity and metabolic syndrome in human subjects[60-65].

Role of vitamin A: Evidences from a genetic obese rat model (WNIN/Ob strain)

I. Study on adult rats

(i) Effect on adiposity: It is well known that adipose tissue mass is tightly regulated by both size and/or number and the latter in turn is regulated by a balanced process of recruitment, differentiation of pre-adipocyte into mature adipocyte (adipogenesis) and adipocyte cell death (apoptosis). Murray and Russell[66] for the first time demonstrated the inhibitory effect of retinoic acid on adipogenesis in 3T3L1 preadipocytes. Subsequently, many studies have shown similar inhibitory effect of retinoids on adipogenesis/adiposity, using both *in vitro* and *in vivo* models, perhaps through different mechanisms[67-72]. However, no study has explored the effect of vitamin A-enriched diet on obesity using either diet-induced or genetic models.

The WNIN/Ob rat strain developed spontaneously from a 90-year-old Wistar-inbred rat stock colony maintained at National Centre for Laboratory Animal Sciences (NCLAS), National Institute of Nutrition (NIN), Hyderabad, India has three phenotypes namely lean (+/+), carrier (+/-) and obese (-/-) and the crossing between carrier rats has resulted in three phenotypes following the classical Mendelian ratio of 1:2:1, respectively. Though, the exact mutation responsible for the obese phenotypes is yet to be identified, Kalashikam *et al*[73] have observed the localization of mutation to a recombinant region upstream of the leptin receptor, *i.e.* 4.3 cM region with flanking markers D5Rat256 and D5Wox37 on chromosome 5. The obese phenotype of this strain is characterized by polyurea, polydypsia, hyperphagia, euglycaemia, hyperleptinaemia, hyperinsulinaemia, hypertriglyceridaemia, hypercholesterolaemia, visceral adiposity (which are akin to human obesity)[74] and elevated plasma high density lipoprotein (HDL)-cholesterol levels. Further, these obese rats are infertile and elicit poor immune response to hepatitis B vaccine[74,75]. When adult male (7 months old) obese rats were fed with vitamin A-enriched diet (*i.e*. as a source of vitamin A, 129 mg retinyl palmitate added per kilogram of diet) for a period of 60 days, significant reductions in body weight gain, adiposity index and visceral fat; retroperitoneal white adipose tissue (RPWAT) were observed without any alteration in their food intake as compared to stock diet-fed obese counterpart[76].

Experiments to understand the mechanism of vitamin A-mediated action have revealed that high doses of vitamin A did not affect the adipocyte size of RPWAT in any of the phenotypes as indicated by adipocyte cell density[76]. On the other hand, vitamin A-induced RPWAT apoptosis was observed in lean rats. Protein expression data showed a significant reduction in anti-apoptotic protein; Bcl2 expression, with a concomitant increase in pro-apoptotic protein; Bax, which was in line with the moderate reduction in adiposity and RPWAT weight[76]. However, in obese phenotypes, there were no such changes in the expression of pro-and anti-apoptoic proteins or their ratio[76].

Further, in obese rats fed with vitamin A-enriched diet, brown adipose tissue-uncoupling protein 1 (BAT-UCP1) expression showed a marked increase, while lean rats did not show such transcriptional activation upon feeding of vitamin A-enriched diet as compared to their respective counterpart receiving a stock diet[77]. It is well established that vitamin A metabolites, particularly, retinoic acid is a potent positive regulator of BAT-UCP1[67,68]. However, in our study, it was not clear as to why lean rats did not have BAT-UCP1 induction by high vitamin A diet feeding. It was presumed that lean rats had a maximal basal expression of UCP1 compared with their age- and sex-matched obese counterparts, which was not further induced by vitamin A supplementation[77]. We have also reported that fatty acid desaturase index; which reflects the stearoyl CoA desaturase1 (SCD1) activity, of plasma and various tissues is well correlated with adiposity and body mass indices of obesity[78]. However, in this study, data from stearoyl CoA desaturase1 gene expression of both liver and adipose tissue revealed that anti-obesity effect of vitamin A was independent of SCD1 regulation, a well-known lipogenic/adipogenic marker[79,80]. Feeding the obese rats of the same strain with identical dose of vitamin A (129 mg per kg diet for 20 wk) resulted in the loss of visceral fat, which was partly attributed to decreased 11β-HSD1 activity resulting in low levels of active metabolites of glucocorticoids[81]. Overall, data from adult WNIN/Ob strain studies demonstrate that vitamin A regulates obesity through visceral fat loss partly by thermogenic and glucocorticoid pathways in obese rat.

(ii) Effect on dyslipidaemia: The most evident systemic problem associated with long-term treatment of retinoic acid for various types of skin disorders and cancer is hypertriglyceridaemia (HTG) and dyslipidaemia[82-84]. Similarly, chronic feeding of vitamin A-enriched diet evoked hypertriglyceridaemia in both lean and obese phenotypes. It is well known that stearoyl CoA desaturase1 is one of the key determinant factors responsible for hypertriglyceridaemia[79,80]. Though lean rats showed a positive association between elevated SCD1 expression and hypertriglyceridaemia by vitamin A feeding, obese rats did not show such association[76]. Retinoic acid-induced hypertriglyceridaemia is shown to be due to both increased hepatic production of very low density lipoprotein (VLDL) and suppression of lipoprotein lipase (LPL) activity in peripheral tissues[83]. We speculate that in obese rats, vitamin A-mediated-hypertriglyceridaemia may be partly due to inhibition of peripheral utilization of VLDL-triglycerides by LPL and/or by increased hepatic production of VLDL.

In obese rats, there was a significant increase in hepatic total lipid, triglycerides (TG) and decrease in phospholipid (PL) contents after feeding with vitamin A-enriched diet[76], whereas in lean rats a similar trend was seen, though not significant. It is known that the initial step is shared by both TG and PL biosynthetic pathways, and therefore, we speculate that vitamin A might increase the hepatic TG synthesis by activating key enzymes involved in TG pathway such as glycerol-3-phosphate dehydrogenase (G3PDH) and diacyl glycerol:acyltransferase (DGAT), which would have hampered the PL synthesis and decreased lipid phosphate contents of liver[76]. We do not have supportive data at present; however, studies are underway to find out the underlying molecular mechanisms.

Obese rats are hypercholesterolaemic with elevated HDL-C levels, partly due to underexpression of hepatic scavenger receptor class B1 (SR-B1), an authentic HDL receptor, which brings about selective uptake of cholesterol esters from HDL particle by liver; the final step in reverse cholesterol transport (RCT) and its subsequent excretion as free cholesterol or bile acids through bile[85]. It was observed that obese rats fed with vitamin A-enriched diet resulted in reduction in circulatory cholesterol level and normalized HDL-C levels, with concomitant upregulation of hepatic SR-BI expression at both protein and gene levels in obese phenotype. The results show vitamin A as a positive regulator of *SR-B1* gene and its role in the regulation of obesity-associated hypercholesterolaemia in obese rats of WNIN/Ob strain[86].

(iii) Effect on retinal degeneration: Various clinical and epidemiological studies have shown the positive association between obesity and age-related macular degeneration (AMD)[87-89]. Previously, Reddy *et al*[90] have shown the progressive retinal degeneration after the onset of obesity in this obese rat strain (WNIN/Ob) due to retinal stress and other factors including impaired tissue remodelling and phototransduction, *etc*. Recently Marcal *et al*[91] have reported that impaired AKT signaling in retina is the key player of the retinal degeneration in diet-induced obese model. We have linked elevated polyol pathway to the cataract development in these obese rats[92]. Improved retinal morphology associated with increased retinal rhodopsin, rod arrestin, phosphodiesterase, transducins, and fatty acid elongase-4 gene expression was observed upon vitamin A-enriched diet feeding (26 & 52 mg per kg diet for about 20 wk). The basal levels in obese rats were found to be low when compared to their age- and sex-matched lean counterparts fed on stock diet containing 2.6 mg vitamin A per kg diet[93]. These observations indicate that specific nutrient supplementation particularly vitamin A may help in the amelioration of retinal degeneration associated with obesity and aging.

II. Study on younger rats

(i) Effect on adiposity & dyslipidaemia: Study on younger rats (50 days old) was done to test the hypothesis that early intervention with vitamin A-enriched diet (129 mg/kg diet) prevents the development of obesity and its associated disorders in the same strain rats *i.e.* WNIN/Ob. At the end of three months, physical (body weight, visceral fat weight and food intake) and biochemical parameters particularly plasma lipid profile (total cholesterol, HDL-C and triglycerides) were in line with those observed in adult rats experiment, in addition to a significant reduction in the epidydimal white adipose pads[94]. As most of the changes were similar to those observed in adult rat experiment, we focused our attention on insulin resistance, which showed significant improvement by high vitamin A-diet feeding, especially in obese phenotype.

(ii) Effect on insulin resistance: As described earlier, obese rats of this strain are euglycaemic and hyperinsulinaemic. Surprisingly, fasting circulatory insulin levels were significantly decreased in obese rats fed on vitamin A enriched diet, while fasting glucose levels remained unaltered, resulting in improved insulin sensitivity index[94]. To understand the mechanism of vitamin A-mediated amelioration of insulin resistance in obese rat, expression of muscle insulin signaling pathway proteins was studied. A significant increase in the ratio of phosphorylated insulin receptor (pIR) to insulin receptor (IR), with concomitant decrease in protein tyrosine phosphatase 1B (PTP1B) levels as compared to their stock diet-fed obese rats was observed[94].

Further, soleus muscle fatty acid composition of obese rats fed on vitamin A-enriched diet revealed that fatty acid desaturation index [the ratio of palmitoleic to palmitic (16:1/16:0) acid of triglyceride (TG) and phospholipid (PL) fractions] showed significant decrease, especially with undetectable 16 : 1 levels of PL fraction, with concomitant decrease in the protein expression of SCD1 in muscle (whose levels were found to be high in control obese rats as compared to their lean counterparts). Vitamin A had no impact on the expression of some important glucogenic, lipogenic and fatty acid oxidative pathway proteins such as phosphoenol pyruvate carboxy kinase (PEPCK), glucose transporter 4 (GLUT4), fatty acid synthase (FAS), long chain fatty acid CoA synthases 4 and 5 (ACSL 4 & 5), fatty acid binding protein (FABP), AMP-activated protein kinase (AMPK)and phosphorylated AMPK (pAMPK)[(94)].

Besides its lipogenic nature, SCD1 is also known to affect the insulin sensitivity[95]. A study on SCD1 knockout mice demonstrated that SCD1 deficiency resulted in decreased PTP1B expression resulting in higher tyrosine phosphorylation of IR, IR substrates 1 and 2, and thus improved glucose clearance and insulin sensitivity[96]. PTP1B is proven to be an important physiological regulator of insulin action, as it directly interacts with IR and attenuates the insulin signaling by dephosphorylating tyrosine phosphorylated proteins. Dysregulation of PTP1B is associated with insulin resistance in both human and experimental animals[97,98].

Summary and future perspectives

Overall, chronic vitamin A-enriched diet feeding significantly impacted the obesity development both in young and adult obese rats of WNIN/Ob strain, possibly through thermogenic and glucocorticoid pathways without eliciting any toxic symptoms. Further, vitamin A improved the HDL-C metabolism by hepatic SR-B1 mediated reverse cholesterol transport mechanism. However, high doses of vitamin A aggravated hypertriglyceridaemia in obese rats

and induced it in lean rats. This is the only negative aspect of vitamin A supplementation study on obesity. Though the mechanism is not known, further studies are in progress to test the minimum effective dose, which brings about the beneficial effects, devoid of deleterious effect, *i.e.* hypertriglyceridaemia in these obese rats. Though, insulin sensitivity status in adult rats by vitamin A was not studied, at younger age long-term vitamin A supplementation was found to be beneficial by improving insulin sensitivity through insulin receptor phosphorylation due to downregulation of PTP1B protein expression. The findings from our studies demonstrate that chronic challenging of obese rats with vitamin A-enriched diet ameliorates obesity and its associated complications by regulating different pathway genes of liver, retroperitoneal white adipose tissue, brown adipose tissue, skeletal muscle and retina (Figure). Importantly, no symptoms of vitamin A toxicity, such as reduced food intake, depressed growth, alopecia, paralysis of legs and occasional bleeding from nose in either of the phenotypes were observed in our studies and impact of vitamin A-enriched diet on some of the clinical and biochemical parameters is given in the summary Table.

Last decade has evidenced extensive research by relating vitamin A status and adiposity, thereby attributing a novel role to this vitamin and lot more functions yet to be unraveled. As of now, no study has addressed the role of vitamin A on inflammation *per se*, associated with obesity and explored the plausible underlying mechanisms. Therefore, impact of vitamin A status/supplementation on the gut microbiome and inflammation in obesity is an important area of research, which has direct implication on human health. Also, its role in other obesity-associated morbidities such as impaired reproductive performance and micro-vascular complications of cardiac and renal systems are largely unexplored. Many studies including ours are mostly centric towards adipose tissue and to some extent to liver and muscle; thereby leaving the other tissue

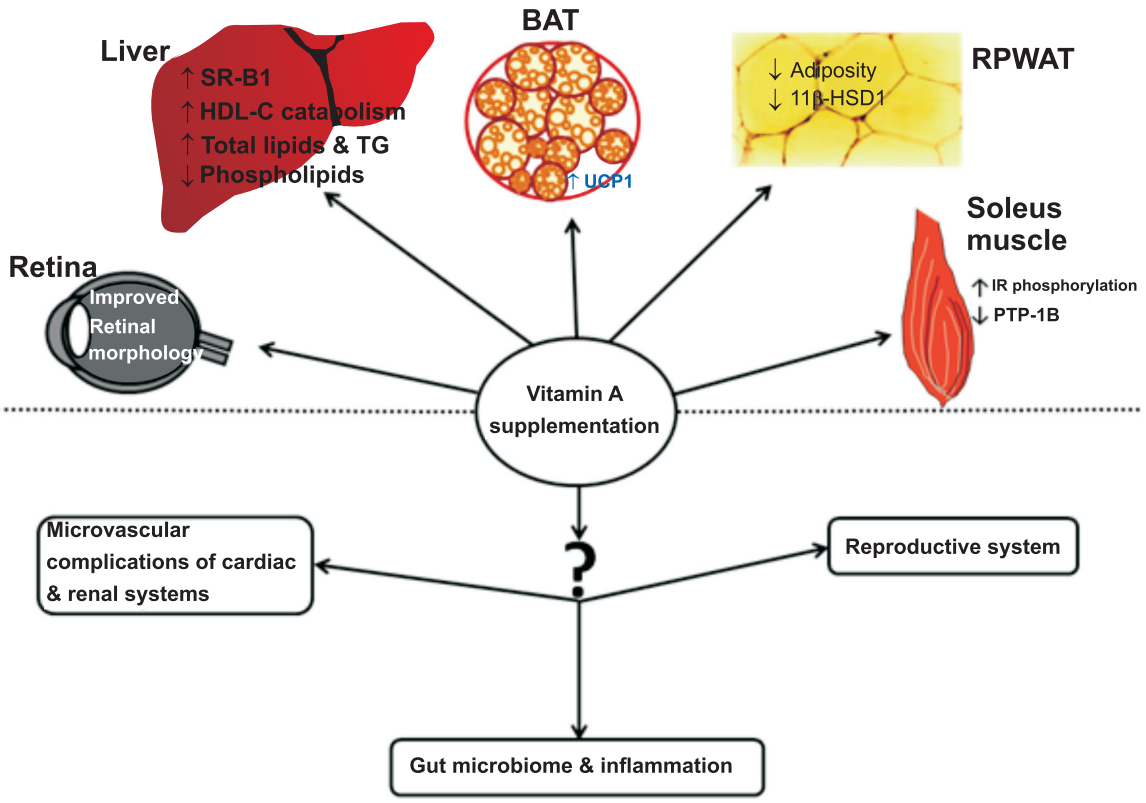

Fig. Impact of vitamin A supplementation on various organs. Schematic picture showing the effect of vitamin A supplementation on obesity and its associated disorders and scope for the further research. RPWAT, retroperitoneal white adipose tissue; BAT, brown adipose tissue; SR-B1, scavenger receptor class B1, UCP1, uncoupling protein 1; 11β-HSD1, 11β-hydroxysteroid dehydrogenase1; IR, insulin receptor; PTP1B, protein tyrosine phosphatase 1B.

Table. Summary of impact of vitamin A-enriched diet on clinical/biochemical parameters

	Study on adult rat				Study on younger rat			
	Lean		Obese		Lean		Obese	
	Control diet	Vitamin A-enriched diet	Control diet	Vitamin A-enriched diet	Control diet	Vitamin A-enriched diet	Control diet	Vitamin A-enriched diet
Body weight	NOR	NC	↑	↓	NOR	NC	↑	↓
Weight gain	NOR	NC	↑	↓	NOR	NC	↑	↓
Food intake	NOR	NC	↑	NC	NOR	NC	↑	NC
RPWAT weight	NOR	NC	↑	↓	NOR	NC	↑	↓
Epididymal WAT weight	NOR	NC	NC	NC	NOR	NC	↑	↓
Serum/plasma retinol	NOR	NC	NC	NC	NOR	NC	NC	NC
Serum/plasma triglycerides	NOR	NC	↑	↑↑	NOR	NC	↑	↑↑
Serum/plasma glucose	NOR	NC	NC	NC	NOR	NC	NC	NC
Plasma insulin	ND	ND	ND	ND	NOR	NC	↑	↓
Serum NEFA	NOR	NC	↑	NC	ND	ND	ND	ND
Serum/plasma total cholesterol	NOR	NC	↑	↓	NOR	NC	↑	↓
Serum/plasma HDL-C	NOR	NC	↑	↓	NOR	NC	↑	↓

NOR, normal; NC, no change; ↑, increase; ↑↑, augmented increase; ↓, decrease and ND-no data; RPWAT, retroperitoneal white adipose tissue; WAT, white adipose tissue; NEFA, non-esterified fatty acids; HDL-C, high denisty lipoprotein cholesterol
Source: Refs 72, 76, 77, 86, 94

physiology unexplored. Hence, the researchers should try to fill-up these knowledge gaps and elucidate the role of vitamin A in maintaining optimal health and alleviation of various disease processes.

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